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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,518	07/06/2001	Keith D. Allen	R-716	3954

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	14

DATE MAILED: 11/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/900,518	Applicant(s) ALLEN ET AL.	
	Examiner Celine X Qian	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *11-16 and 22-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 17-21* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-28 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the inventions Group I-XI are related and a search and examination of all 11 groups can be made without serious burden. This is not found persuasive. The inventions of Groups I-XI are patentably distinct for reasons set forth of the record mailed on 9/9/02. Although the inventions are related, a search of one invention is not co-extensive with the search of another. Therefore, a search of all 11 Groups is burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 11-16 and 22-28 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-10 and 17-21 are currently under examination.

Claim Objections

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim is drawn to a construct comprising a screening marker. Since it's unclear how it is different from the "selection marker," claim 2 fails to limit the subject matter of claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-10, 17-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous knockout mouse comprising a disruption in the carboxypeptidase X2 (CX2) gene, wherein both alleles are inactivated, and exhibiting phenotypic features such as increased body length, tolerance to glucose, ability to metabolize glucose and decreased threshold response to metrazol as compared to wild type mice, a method of producing such a transgenic mouse, and a cell isolated from the knockout mouse, does not reasonably provide enablement for other transgenic and/or knockout animals comprising any disruption in a CX2 gene. Further, the specification is not enabling for a knockout mouse comprising any disruption in CX2 gene nor for a cell comprising any disruption in a CX2 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 5-10, 17-21 are drawn to a cell comprising a disruption in the CX2 gene, a non-human transgenic animal comprising a disruption in the CX2 gene, a cell from that transgenic animal, and a method of producing the mouse with a disruption in said gene. Thus, the nature of the invention is directed to transgenic animals and methods of producing the transgenic animals.

Breadth of Claims:

In the instant case, claims 5-10, 17-21 encompass any transgenic animal containing any disrupted allele for the gene that encodes the CX2. Further, the claims encompass any knockout mouse comprising any disruption in CX2 gene and exhibiting the phenotypes of increased body length, tolerance to glucose ability to metabolize glucose and decreased threshold response to metrazol as compared to wild type mice. Further, the claims encompass any cell comprising any disruption in the CX2 gene and encompass all cells capable of undergoing homologous recombination (specification page 7, line 4-6). The disruption, as disclosed in the specification (page 6, lines 30-34, page 7, lines 1-3) includes any insertion, deletion or substitution in any portion of the gene (introns, exons, regulatory regions). The claims, therefore, encompass all such disruptions and also cover all animals that contain a CX2 gene disruption (page , lines 4-6).

The specification does not provide an enabling disclosure for the full scope of transgenic animals of the type claimed. The only embodiment enabled by the specification within the scope of claims 5-10, 17-21 is for a homozygous knockout mouse comprising a disruption in the CX2 gene that results in loss of function of the CX2 gene and exhibiting phenotypic features such as increased body length, tolerance to glucose, ability to metabolize glucose and decreased threshold response to metrazol as compared to wild type mice, a method of producing such a transgenic mouse. Thus the scope of the claims is very broad and encompasses any transgenic

animal and a knockout mouse with any disruption in the CX2 gene and includes any and all mutant forms, substitutions, deletions, or insertions in the CX2 gene (specification, pages 6 and 7, bridging paragraph, lines 30-34, lines 1-3).

Amount of guidance in the specification and Working Examples:

The specification discloses the use of the CX2 gene as set forth in SEQ ID NO:1 in producing a homozygous transgenic knockout mouse, wherein the knockout mouse exhibits phenotypic changes that include increased body length, tolerance to glucose, ability to metabolize glucose and decreased threshold response to metrazol as compared to wild type mice.

The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that encodes a murine CX2 gene of SEQ ID NO:1 wherein the disruption results in loss of function of the CX2 gene. The specification does not teach how to make and use the invention with other species of transgenic or knockout animals and with any knockout mouse with any form of disruption in the gene encoding CX2, as claimed in the claims 5-15, 17-21. Further, the specification does not teach how to make and use any cell comprising any type of disruption in the CX2 gene as claimed. The scope of claims 5-10, 17-21 thus surpasses that enabled by the specification.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention with any and all transgenic animals as claimed. The specification and the

working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two inactivated alleles for the gene that encodes a murine CX2 wherein the knockout mice exhibit increased body length, tolerance to glucose, ability to metabolize glucose and decreased threshold response to metrazol as compared to wild type mice. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all transgenic animals and/or transgenic mice carrying any and all transgene(s) of the types recited in the claims.

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses the phenotype of a homozygous CX2 gene knockout mouse comprising a disruption in the CX2 gene comprising the sequence set forth in SEQ ID NO:1 and fails to disclose the phenotypes of other species of knockout animals with a disruption in the CX2 gene. Given the state of the art, the phenotype of any transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out animals, including mice, that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification.

Further, transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). Thus, while the specification is enabled for a homozygous knockout mouse containing two inactivated alleles for the gene comprising the

sequence set forth in SEQ ID NO:1 and encoding the CX2, wherein the mouse exhibits increased body length, tolerance to glucose, ability to metabolize glucose and decreased threshold response to metrazol as compared to wild type mice, does not provide sufficient support for the same transgene-dependent phenotype in other animal systems.

The particular genetic elements required for expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, the phenotype of knockout animals is not predictable. For example, Jacks et al. (1992) describe Rb knockout mice that do not display retinoblastoma; rather they exhibit the unexpected phenotype of pituitary tumors. The pituitary tumors arise from cells lacking a wild-type Rb allele. Thus, tumors were found to arise not in retinas, as in humans, but in the pituitary gland (page 299, Discussion, paragraphs 1 and 3). Therefore, in the absence of specific guidance and working examples, the phenotype of transgenic animals with the scope as claimed is unpredictable. In such a situation, one skilled in the art would not know how to make and use the invention as claimed, without undue experimentation.

The specification fails to provide an enabling disclosure for the preparation of other species of knockout animals besides mice having a disruption in the CX2 gene because the guidance offered in the specification is limited to the preparation of mice harboring such mutations and no teachings or guidance are offered in regard to how one would have prepared any other type of animal having the recited gene disruption. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out the method. There is no evidence to support

that a transgenic knockout mouse can be generated by using other types of cells comprising a disrupted gene. The only species in which such technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Likewise, Mullins et al. (1996) teach that "[a]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p. S38, column 1, paragraph 1). Thus, knockout animals cannot be prepared for any species other than the mouse. Since ES cell technology was required to produce the claimed animals and practice the claimed methods of using such animals, in the absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed animals and to practice the claimed methods in species other than mice.

In view of the limited guidance in the specification, and limited working examples directed to transgenic, knockout mice with a specific knockout gene and exhibiting a specific phenotype, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to make and use the invention in its full scope as claimed. Thus, the enabled scope of the claims is limited to a homozygous knockout mouse comprising a disruption in CX2 gene, whereby such disruption does not produce a functional CX2 protein and

exhibiting phenotypic features of increased body length, tolerance to glucose, ability to metabolize glucose and decreased threshold response to metrazol as compared to wild type mice, and a method of producing such a transgenic mouse.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 9, 10 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1-4 and 10, it is unclear how the target construct is arranged. In other words, is the first polynucleotide adjacent to the second polynucleotide or there is a selectable marker in between? Where is the screening marker located in the construct? In addition, it is also unclear whether the first and second polynucleotide is a contiguous sequence of the target gene or just portions of the target gene. The arrangement of the elements is essential to the operability of the invention.

Regarding claims 1-4, the terms "selectable marker," "selection marker" or "screening marker" render the claim indefinite because it is unclear how a marker protein can be inserted in a vector construct. Use of term such as "selectable marker gene" is suggested.

Regarding claim 2, the term "screening marker" renders the claim indefinite because it is unclear what term encompasses. In other words, it is unclear how a "screening marker" differs from the "selection marker" recited in claim 1.

Regarding claims 9 and 21, the word "derived" renders the claim indefinite because the nature and number of derivative processes is unknown. Use of the term "isolated" is suggested.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
November 4, 2002

Anne-Marie Falk
ANNE-MARIE BAKER
PATENT EXAMINER